III. Remarks

A. Formal Matters

Claims 44-53 are currently pending in this application. Claims 1-43 were previously canceled. Applicants herein amend claim 44 strictly for the purpose of expediting prosecution and amend claims 45-47 and 50-53 to provide a proper antecedent basis for each claim. Upon entry of these amendments, claims 44-53 are under active consideration. Applicant respectfully requests entry of the amendments and remarks made herein into the file history of the present application. The Examiner, in the Advisory Action, denied entry of the amendments filed in Applicants' response to the Final Office Action, filed December 22, 2006. *See* Advisory Action, page 1. The amendments made herein replace those filed in Applicants' response to the Final Office Action.

Applicants herein amend the paragraph beginning at page 183, line 1 of the specification to capitalize the trademark used therein. Applicants respectfully submit that the trademark used therein is "ULTRAFREE-MC" and not "Millipore" as stated by the Examiner in the prior Office Action dated November 11, 2000. Millipore is the manufacturer and, as such, there is no requirement that the name be capitalized.

Applicants herein amend the paragraph beginning at page 173, line 9 of the specification to capitalize the trademark used therein.

In view of the application as originally filed providing support for each of the amendments made herein, Applicants respectfully submit that no new matter has been added.

B. Patentability Rejections

1. The Rejections Under 35 U.S.C. §112, First Paragraph – Written Description – Should be Withdrawn

The Examiner, in the Final Office Action mailed July 5, 2006, maintained the rejection of claims 44 and 46 under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. *See* Final Office Action, page 3. The Examiner alleged that the instant specification does not provide sufficient written

description to show possession of the entire genus of binding pairs, maintaining that the instant specification "only discloses examples of one type of specific binding pair, antibodies."

Applicant, in the response to the Final Office Action, respectfully submitted that the Examiner improperly construed the term "specific binding pair" and consequently improperly construed claims 44 and 46. Applicant also respectfully submitted that the instant application contains experimental exemplification of the display of a wide variety of members of different specific binding pairs of different structure and function and provided support in the specification for seven specific binding pairs including antibody-antigen, enzyme-substrate and receptor-ligand binding pairs. Finally, Applicant pointed out to the Examiner that in each of the aforementioned binding pairs, one specific binding pair member is displayed on the surface of a phage and demonstrated to form a specific binding pair with its respective complementary binding member, as reflected in the recitation of "a" specific binding pair member in pending claim 44.

The Examiner, in the Advisory Action mailed January 29, 2007, maintained the rejections of record. *See* Advisory Action, page 2.

a. 35 U.S.C. § 112, First Paragraph - Scope of the Claims

Applicants respectfully submit that the Examiner has mischaracterized the scope of the claimed invention by failing to take into account the teachings of the entire specification. As a first step in determining compliance with 35 U.S.C. § 112, first paragraph, the Examiner is instructed to determine the scope of each claim. See Guidelines for the Examination of Patent Applications under the 35 U.S.C. § 112, first paragraph, "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111 (the "Written Description Guidelines"). Each claim is to be given its "broadest reasonable interpretation in light of and consistent with the written description." *See* Written Description Guidelines at page 1105 (emphasis added). Examiners are then to determine from the standpoint of one of skill in the art at the time the application was filed whether there is sufficient disclosure to show possession of the claimed invention as a whole. *See* Written Description Guidelines at page 1105.

The Examiner, in the Final Office Action and the Advisory Action has repeatedly mischaracterized the scope of pending independent claim 44 and subsequently applied

this mischaracterization to dependent claims 45-53. *See*, e.g. page 3 of the Advisory Action where the Examiner alleges that "[c]ontrary to applicant's assertion, the claims (especially Claim 44) as written encompasses the cells displaying both members of the binding pair, as discussed in the previous Office action, 7/5/06, pp. 3+ and pp. 7+."

Quite simply stated, the claims did not and do not encompass cells displaying both members of the binding pair. Pending claim 44, as currently amended, is directed to "recombinant host cells each of which harbors a nucleic acid fragment encoding a specific binding pair member." The instant specification describes a "specific binding pair" at page 27, line 23 through page 28, line 5 as follows:

> This describes a pair of molecules (each being a member of a specific binding pair) which are naturally derived or synthetically produced. One of the pair of molecules, has an area on its surface, or a cavity which specifically binds to, and is therefore defined as complementary with a particular spatial and polar organization of the other molecule, so that the pair have the property of binding specifically to each other. Examples of types of specific binding pairs are antigen-antibody, biotin-avidin, hormone-hormone receptor, receptor-ligand, enzyme-substrate, IgG-protein A.

The above description is consistent with the use of the term throughout the specification. According to the specification, and as is known by one of ordinary skill in the art, phage display provides a method for detecting protein-ligand interactions. For example, a population of proteins containing a protein of interest (one member of the binding pair) may be displayed on the surface of the bacteriophage particles and screened against a potential ligand (potential complementary member of the binding pair) in order to obtain a protein of interest which specifically binds to the ligand. (As an example, an enzyme of interest that binds a substrate can be obtained.) This is described at length throughout the specification, and illustrated schematically in Figure 2. One of ordinary skill in the art fully understands that an interpretation of claim 44 to include the display of both members of a specific binding pair on the phage surface would defeat the purpose of phage display and is not a reasonable interpretation of pending claim 44 in light of the specification.

As indicated by the plain language of pending claim 44, the present invention relates to the bacteriophage display of a member of a specific binding pair, i.e., "a

specific binding pair member" on bacteriophage particles produced by each host cell. A "pair" is composed of two molecules, each of which binds the other. An antibody binds an antigen – thus antibody and antigen represent a specific binding pair. An antibody is a member of a specific binding pair, wherein the pair is composed of antibody and antigen. Similarly, an enzyme and substrate represent a specific binding pair. To act on its substrate an enzyme must bind that substrate. An enzyme is a member of a specific binding pair, wherein the pair is composed of enzyme and substrate. Similarly, a receptor and ligand represent a specific binding pair in which the receptor binds the ligand. The receptor is a member of a specific binding pair, wherein the pair is composed of the receptor and its ligand. Thus, Applicant respectfully submits that Examiner's characterization of the scope of claim 44 to encompass cells displaying both members of a binding pair is contrary to the plain language of pending claim 44.

b. A Wide Variety of Members of Specific Binding Pairs are Described

Applicant respectfully points out to the Examiner that the instant application contains experimental exemplification of the display of a wide variety of members of different specific binding pairs (one member displayed on bacteriophage of each cell) which differ widely in structure and function, including:

1) Phage-displayed anti-lysozyme VH domain is shown to form a specific binding pair with lysozyme, its complementary binding pair member. *See* Example 4;
2) various phage-displayed antibody scFv domains are each shown to form a specific binding pair with its complementary antigen binding pair member. *See* Examples 4, 6, 8, 9, 13, 18, 21, 23, 25, 29, 43 and 45;
3) phage-displayed PDGF receptor (hereinafter "PDGF-R") is shown to form a specific binding pair with its complementary binding pair member, PDGF ligand. *See* Examples 15 and 16;
4) phage-displayed staphylococcal nuclease is shown to form a specific binding pair with its complementary binding pair member, single stranded DNA substrate. *See* Example 36;

5) either of two amino-terminal domains of phage-displayed human CD4 is shown to form a specific binding pair with its complementary binding pair member, gp120 ligand. *See* Example 37;
6) various phage-displayed antibody Fab fragments are each shown to form a specific binding pair with its respective complementary antigen binding pair member. *See* Examples 7, 25, 26, 27, 33 and 41;
7) phage-displayed antibody Fv fragment is shown to form a specific binding pair with its respective complimentary antigen binding pair member. *See* Example 39; and
8) phage-displayed alkaline phosphatase is shown to form a specific binding pair with its complementary binding pair member, 4-nitrophenyl phosphate substrate. Catalytic activity (i.e., hydrolysis of 4-nitrophenyl phosphate) demonstrates that the enzyme is displayed as a functional dimer. *See* Examples 11, 12, 30, 31 and 32.

In each of the aforementioned cases, a specific binding pair member was displayed on the surface of a phage and was shown to be able to form a specific binding pair with its respective complementary binding member.

In view of the foregoing, which demonstrates the display of a wide variety of members of different specific binding pairs having different structures and functions, it is clear that one of ordinary skill in the art would know that Applicant was in possession of the invention as claimed, at time of filing the Application. Accordingly, Applicants hereby request that the rejection for lack of written description support be reconsidered and withdrawn.

2. **The Rejections Under 35 U.S.C. §112, First Paragraph – Enablement – Should be Withdrawn**

The Examiner, at page 7 of the Final Office Action, maintained the rejection of claims 44 and 45 under 35 U.S.C. §112, first paragraph, for an alleged lack of enablement. The Examiner based this rejection on his allegation that "[t]he only examples provided in the specification are phage displaying antibodies." Further, the

Examiner alleged that, aside from phage displaying antibodies, "no other examples" of binding pairs are provided by the specification.

Applicants, in the response to the Final Office Action, pointed out to the Examiner that the present invention relates to the display of a member of a specific binding pair, i.e., "a specific binding pair member" and not "methods of displaying 'binding pairs' on phage surface" as stated by the Examiner at page 9 of the Final Office Action. Applicant further pointed out to the Examiner that the instant specification discloses phage displaying a broad range of specific binding pair members, each of which is shown to bind to its respective complementary binding partner, demonstrating the functionality of each specific binding pair member (i.e., each binding pair member is folded correctly so as to be able to bind the complementary other member of the specific binding pair).

The Examiner, in the Advisory Action mailed January 29, 2007, maintained the rejections of record. *See* Advisory Action, page 2, bridging page 3. Specifically, the Examiner continues to allege that "the specification, while being enabling for recombinant cells harboring library of specific binding pair member comprising single chain antibody, does not reasonably provide enablement for recombinant cells harboring any other specific binding pair members."

Applicant again directs the Examiner's attention to the specific experimental exemplification of no less than four separate non-antibody molecules of different structure and character expressed in functional form on the surface of phage particles: (i) PDGF-R; (ii) CD4; (iii) staphylococcal nuclease; and (iv) alkaline phosphatase. The specification also provides experimental exemplification of two-chain antibody fragments, specifically, Fab and Fv fragments, in addition to scFv and VH domains.

PDGF-R and CD4, two receptors of different structure and character, are shown to be displayed on phage surface and demonstrated to interact with ligands gp120 and PDGF isoform BB, respectively, to form a specific binding pair. *See* Examples 15 and 16 for PDGF-R, with results shown in Figures 18, 19, 20 and 21, which confirm display of PDGF-R on the phage surface and its specific binding to its complementary specific binding pair member, PDGF isoform BB. *See* Example 37 for CD4, with experimental

results shown in Figure 43, demonstrating display of CD4 on the phage surface and specific binding to its complementary specific binding pair member gp120.

Staphylococcal nuclease is shown to be displayed on phage surface and is demonstrated to specifically bind to its complementary specific binding pair member, substrate single stranded DNA to form a specific binding pair. *See* Example 36. Notably, the phage-displayed staphylococcal nuclease was catalytically active as measured by ability of phage displaying the enzyme to catalyze the cleaveage of single stranded DNA.

Alkaline phosphatase monomer is shown to be displayed on phage surface and demonstrated to bind to its complementary binding member, non-displayed alkaline phosphatase monomers (as measured by activity of the resulting dimer). *See* Examples 11, 12, 30, 31 and 32. Notably, the resulting alkaline phosphatase dimer was demonstrated to be catalytically active, indicating that phage-displayed alkaline phosphatase monomer was correctly folded and functional.

Thus, a wide variety of phage-displayed structurally and functionally unrelated polypeptides are each demonstrated to form a specific binding pair with its complementary (non-displayed) binding pair member,

Finally, Applicant reiterates that, contrary to the Examiner's allegation at page 10 of the Final Office Action, the instant specification does NOT provide evidence that phage display cannot be easily generalized to other proteins. Specifically, the Examiner points to the specification, beginning at page 10, line 9, which allegedly recites an example of an unsuccessful attempt to display bovine pancreatic trypsin inhibitor. Applicants respectfully submit that Examiner has misread the specification. In relevant part, the specification states that "the proposal was not shown to be operative." See instant specification, page 10, lines 12-13. The proposal was not shown to be inoperative either – in fact WO90/02809 contains no experimental evidence at all, only hypothetical conjecture. There is no statement that the display was unsuccessful. In contrast to the Examiner's allegation, a wide variety of displayed proteins is demonstrated experimentally in the instant specification, as well as their ability to bind a relevant complementary specific binding pair member, such as an antigen, ligand, or substrate.

Accordingly, Applicants respectfully request that the rejection for lack of enablement be reconsidered and withdrawn

3. The Rejections Under 35 U.S.C. §112, Second Paragraph Should be Withdrawn

The Examiner, at page 10 of the Final Office Action, rejected claims 44-53 as amended under 35 U.S.C. §112, second paragraph, as allegedly being indefinite. Specifically, the Examiner alleged that it is unclear: (1) if each recombinant cell comprises one member of a binding pair or both members; (2) of what entity "a binding domain" is comprised; and (3) of what entity "genetic material" is comprised.

Applicants, in the response to the Final Office Action, stated their belief that the claims did not lack clarity. However, in the interest of expediting prosecution of the application, applicant filed amendments which, according to the Advisory Action, were not entered.

While Applicants continue to believe, as discussed *supra*, that the pending claims do not lack clarity, in the interest of expediting the prosecution of the instant application, Applicants herein amend claim 44 as follows: (1) each of the claimed recombinant host cells harbors a nucleic acid that encodes one member of a specific binding pair; (2) the members of specific binding pairs (and clearly not the bacteriophage particles) comprise the "binding domain"; and (3) the term "genetic material" refers to that of the bacteriophage particle. Claims 45-47 and 50-53 are amended to provide a proper antecedent basis for each claim.

In light of the foregoing claim amendments and discussion Applicants respectfully submit that one of ordinary skill in the art would easily determine the metes and bounds of the claimed invention. Accordingly, Applicants request reconsideration and withdrawal of the rejection of claims 44-53 under 35 U.S.C. §112, second paragraph.

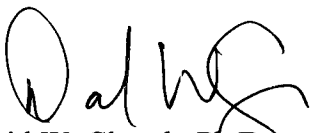
C. Conclusion

In view of the above amendments and remarks, Applicants respectfully submit that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone

conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

HOWREY LLP

By: 

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